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Original Article

Sleep variability and cardiac autonomic modulation in adolescents – Penn State Child Cohort (PSCC) study

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ABSTRACT

Objective: To investigate the effects of objectively measured habitual sleep patterns on cardiac autonomic modulation (CAM) in a population-based sample of adolescents.
Methods: We used data from 421 adolescents who completed the follow-up examination in the Penn State Children Cohort study. CAM was assessed by heart rate (HR) variability (HRV) analysis of beat-to-beat normal R-R intervals from a 39-h electrocardiogram, on a 30-min basis. The HRV indices included frequency domain (HF, LF, and LF/HF ratio), and time domain (SDNN, RMSSD, and heart rate or HR) variables. Actigraphy was used for seven consecutive nights to estimate nightly sleep duration and time in bed. The seven-night mean (SD) of sleep duration and sleep efficiency were used to represent sleep duration, duration variability, sleep efficiency, and efficiency variability, respectively. HF and LF were log-transformed for statistical analysis. Linear mixed-effect models were used to analyze the association between sleep patterns and CAM.
Results: After adjusting for major confounders, increased sleep duration variability and efficiency variability were significantly associated with lower HRV and higher HR during the 39-h, as well as separated by daytime and nighttime. For instance, a 1-h increase in sleep duration variability is associated with –0.14(0.04), –0.12(0.06), and –0.16(0.05) ms^2 decrease in total, daytime, and nighttime HF, respectively. No associations were found between sleep duration, or sleep efficiency and HRV.
Conclusion: Higher habitual sleep duration variability and efficiency variability are associated with lower HRV and higher HR, suggesting that an irregular sleep pattern has an adverse impact on CAM, even in healthy adolescents.

1. Introduction

Due to the modern, around-the-clock lifestyles, many people form poor habitual sleep patterns and experience sleep disturbances and sleep deprivation. A number of epidemiological studies have demonstrated that sleep disturbance and short sleep duration are associated with adverse cardiovascular outcomes, such as hypertension, diabetes, and obesity [1–6]. Additionally, a recently published meta-analysis in adults demonstrated that short sleep duration was associated with increased risk of coronary heart disease mortality [7]. Not only is short sleep duration common among adults, but it is also a growing problem even among children and adolescents [8–10]. Recent studies have reported that, on average, adolescents sleep <8 h per night, which is less than the recommended 9 h of sleep [11–14]. More importantly, short sleep duration has been associated with disrupted autonomic nervous system function, a predictor of cardiovascular diseases (CVDs), in children [15,16]. As children and adolescents are in a developmental period and at a critical time of forming sleep habits, they may benefit by acquiring the habit of getting enough sleep and consequently reduce CVD risk in adulthood. However, the vast majority of the previous studies were based on subjectively reported sleep duration instead of objectively measured sleep duration. As subjectively

Abbreviations: BMI, Body mass index; CAM, Cardiac autonomic modulation; CVD, Cardiovascular diseases; EGC, Electrocardiography; HF, High-frequency range; HR, Heart rate; HRV, Heart rate variability; LF, Left frequency range; LF/HF, The ratio of LF to HF; PSCC, Penn State Children Cohort; PSG, Polysomnography; RMSSD, Square root of the mean of the sum of the squares of differences between adjacent RR intervals; SD, Standard deviation; SDNN, Standard deviation of all RR intervals.

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measured sleep duration is weakly correlated with objective sleep duration, one can argue that subjectively measured sleep duration may serve as a surrogate of stress, anxiety, and depression. Thus, the association between subjectively measured short sleep duration may be biased by psychological conditions of the participants.

On the other hand, with increased availability of noninvasive methods of monitoring multiple nights of sleep, like actigraphy, objectively measured habitual sleep patterns, such as the variability in sleep duration or sleep efficiency (the percentage of actual sleep duration during the total time in bed), have been utilized in sleep studies [17–21]. Although there is very little direct evidence linking habitual sleep patterns and CVD risk, it has been associated with CVD risk factors, such as insomnia [19,22,23]. Specifically, if someone does not sleep enough on one night, then that person may try to sleep longer the next night in an attempt to “recover” the sleep that was lost. Although the so-called “recovery” sleep may provide some temporary improvement, it could also result in less total sleep time or lower sleep efficiency on subsequent nights, as too much “recovery” sleep may paradoxically impair the ability to fall asleep on the next night [23,24]. More important, our group has reported an association between insomnia symptoms and impaired heart rate variability (HRV) in children [22]. Therefore, it is plausible that high variability in habitual sleep pattern may lead to impaired cardiac autonomic modulation (CAM).

Heart rate variability HRV is commonly used as a noninvasive measurement of CAM [25], and is regulated by the balance of sympathetic and parasympathetic modulation. Lower HRV calculated from short-term normal RR intervals, ranging from minutes to hours has been associated with CVD mortality and morbidity in various populations [26–32]. The associations between habitual sleep patterns and CAM in adolescents have not been fully understood. In recent years, only two epidemiological studies have reported association between short sleep duration and cardiac autonomic dysfunction in children [15,16]. However, these studies only examined the effect of mean sleep duration, but not the variability, on CAM. Thus, the objective of this study is to investigate, in a population-based-sample of adolescents, the association between objectively measured habitual sleep patterns (mean sleep duration, sleep duration variability, mean sleep efficiency, and sleep efficiency variability) and CAM.

2. Methods

2.1. Study population

We used available data from 421 adolescents who completed the follow-up examination of the Penn State Children Cohort (PSCC) study. The recruitment and examination procedures for the baseline study have been published elsewhere [18]. During 2010–2013, a follow-up examination was conducted. Among the 700 baseline study participants, 421 of them completed the follow-up examination, with a response rate of 60% and a mean (standard deviation or SD) follow-up time of 7.7 (1.4) years. The loss to follow-up was mainly due to subjects moving out of central Pennsylvania. However, no major difference in baseline characteristics was observed between subjects who did and did not participate. During the study period, participants were evaluated overnight in the Clinical Research Center at the Pennsylvania State University College of Medicine including a complete physical examination, a whole body dual-energy X-ray absorptiometry, and a 9-h fixed-time polysomnography (PSG) recording. Blood, saliva, and urine samples were collected after the overnight fasting. After being released from the overnight stay, they were given a set of questionnaires about habitual behavior, and an activity log. A high-fidelity Holter electrocardiogram (ECG) monitor was used to record beat-to-beat ECG during the overnight stay and 24 h after the participant was released, resulting in a total of 39 h recording.

To collect objective night-to-night sleep data, participants wore an actigraph tri-axis accelerometer monitor (GT3X+, Actigraph LLC, Pensacola, FL, USA) for eight consecutive nights (including the night at the sleep laboratory during the PSG) on their wrist of the nondominant hand during bedtime, in conjunction with a sleep diary that recorded “bed time” and “out of bed time” on nightly basis. The actigraphy data were exported to a designated computer for analysis. After an experienced investigator removed the artifacts from the actigraphy data, the total sleep time in bed and the actual sleep duration were obtained by using ActLife 6 software (Actigraph LLC, Pensacola, FL, USA). Sleep data for the first night were excluded from the analysis, as they were measured in a controlled setting under a 9-h fixed sleep protocol. Thus, seven consecutive nights of sleep data were used in this report. The study protocol was approved by Pennsylvania State University College of Medicine IRB. Written informed consent was obtained from participants and their parents if participant was a minor (<18 years old).

2.2. Sleep variables

We objectively assessed the habitual sleep pattern for each participant by using seven-night actigraphy data. After carefully examining and removing any artifacts from the actigraphy data, the following sleep parameters were directly calculated for each night: (1) total in bed time; (2) the total sleep time; and (3) sleep efficiency, which is the percentage of actual sleep duration during the total time in bed [(Sleep duration/Time in bed)*100%]. Based on the total sleep time and sleep efficiency in seven consecutive nights, we calculated the following variables to represent the participants' habitual sleep pattern: (1) the mean of total sleep time as habitual sleep duration; (2) the SD of the mean sleep duration as habitual sleep duration variability; (3) the mean of sleep efficiency as habitual sleep efficiency; and (4) the SD of the mean sleep efficiency as the habitual sleep efficiency variability. Participants with less than five (<5) nights, that is, less than 70% of seven nights, of sleep data were excluded from this report.

2.3. Continuous Holter ECG recording

A high-fidelity (sampling frequency 1000 Hz) 12-lead HScribe Holter System (Mortara Instrument, Inc., Milwaukee, WI, USA) was used to collect the 39-h Holter beat-to-beat ECG data. The high-fidelity ECG significantly increases the resolution and enhances the accuracy of various waveform measurements. All Holter recordings started between 5:00 PM and 7:00 PM. The Holter ECG data were scanned to a designated computer for offline processing by an experienced investigator using specialized SuperECG software (Mortara Instrument, Inc., Milwaukee, WI, USA). The standardized operation procedures for the PSCC study were followed rigorously in the data collection, offline processes, HRV analysis, and interpretation processes. Briefly, the Holter ECG Data Collection and Analysis Procedures were followed to prepare, hook up, calibrate, and start the Holter digital recorder. After 39 h of recording, a trained investigator retrieved and archived the beat-to-beat ECG data for offline processing. The main objective of the offline processing was to verify the Holter-identified ECG waves and to identify and label additional electronic artifacts and arrhythmic beats in the ECG recording. Finally, a single research investigator performed beat-to-beat HRV analysis using the normal beat-to-beat RR interval data.

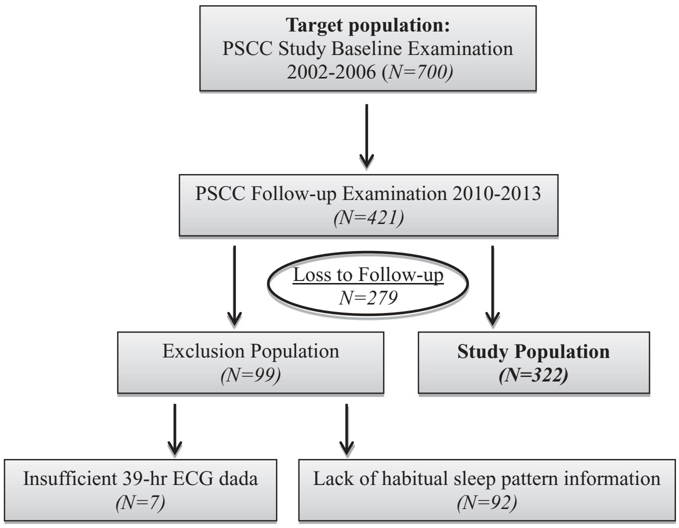

Fig. 1. Penn State Children Cohort (PSCC) study flow-chart.

2.4. *Other covariate*

Demographic information of population attributes, such as age, race, gender, body mass index (BMI) percentile, and medical history were collected at the clinic by an experienced investigator.

2.5. *CAM measures*

The entire 39-h Holter beat-to-beat ECG data (from 5:00PM of Day-1 to 8:00AM of Day-3) were used for this report. The 39-h normal beat-to-beat RR interval data was divided into 30-min segments of RR data. Thus, each individual provided up to 78 segments of 30-min RR data. The RR data for HRV analyses were processed according to current recommendations [28]. Within each segment, any RR interval ≤300 ms, ≥1600 ms, or where the ratio from two adjacent RR intervals was <0.75 or >1.33 were excluded from the HRV analysis. The time and frequency-domain HRV analysis were performed on the remaining normal RR interval data if the total length of such normal RR intervals was >22.5 min (ie, 75% of 30-min segment), using the HRV Analysis Software v1.1 [33]. For the frequency-domain HRV analysis, we used fast Fourier transformation (FFT). Briefly, the adjacent RR interval data were interpolated using a piecewise cubic spline approach, with a 2-Hz sampling rate. The FFT was performed on the equidistantly interpolated RR time series. The following HRV indices were calculated as measures of CAM: power in the high-frequency range (HF, 0.15–0.40 Hz), power in the low-frequency range (LF, 0.04–0.15 Hz), the ratio of LF to HF (LF/HF), standard deviation of all RR intervals (SDNN, ms), and the square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD, ms). Following current recommendations [28], we performed logarithmic transformations on HF and LF for statistical analysis.

2.6. *Statistical analysis*

The characteristics of the study population (mean [SD] or proportions) were calculated. Among the 421 adolescents who completed the follow-up examination, seven individuals with insufficient ECG data and 92 individuals with insufficient habitual sleep information were excluded from the analysis. As a result, the effective sample size for this report is 322 (see Fig. 1). Each individual contributed up to 78 segments of 30-min RR interval data, resulting in 20,984 segments of HRV data. To assess the association between sleep variability and the HRV variables, we used multivariable adjusted linear mixed-effect models. Age, race, gender, and BMI percentile were adjusted in these models. All results from the regression models were expressed as 1-h increase in sleep duration and its variability, or a 10% increase in sleep efficiency and its variability. A *p*-value of ≤0.05 was used to determine statistical significance. All analyses were performed using SAS version 9.3 software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. *Characteristics of study population*

The overall and gender-specific characteristics of the study population are shown on Table 1. Among the 322 adolescents studied, 51.6% ($N = 166$) were males and 79.2% ($N = 255$) were non-Hispanic white. The age and BMI percentile of the entire cohort was 16.7 (2.3) years and 66.2(28.0), respectively. The prevalence of sleep-disordered breathing was 9.6% ($N = 31$). The average sleep duration for males

Table 1
The study population characteristics and summaries of HRV indices.

Demographics	All ($N = 322$)	Male ($N = 166$)	Female ($N = 156$)	*p*-Value
Age (years)	16.7 (2.3)	16.5 (2.3)	16.9 (2.2)	0.09
Non-Hispanics White (%)	79.2	82.5	75.64	0.13
BMI Percentile	66.2 (28.0)	63.6 (30.3)	68.3 (25.9)	0.14
SDB (%)	9.6	13.2	5.8	0.02
Sleep Variables:				
Sleep Duration (hrs)	7.0 (0.8)	6.8 (0.8)	7.1 (0.9)	<0.01
Sleep Duration Variability (hrs)	1.2 (0.6)	1.1 (0.54)	1.2 (0.6)	0.12
Sleep Efficiency (%)	82.54 (6.2)	81.4 (6.7)	83.8 (5.3)	<0.01
Sleep Efficiency Variability (%)	7.0 (4.2)	6.6 (4.4)	7.1 (4.1)	0.69
Weekdays (5 nights)	6.9 (0.9)	6.7 (0.8)	7.1 (0.9)	<0.01
Weekend (2 nights)	7.2 (1.4)	7.1 (1.3)	7.3 (1.4)	0.26
HRV Indices*:				
Log of HF (ms^2)	6.0 (0.9)	5.9 (0.9)	6.0 (0.9)	0.49
Log of LF (ms^2)	6.6 (0.7)	6.6 (0.7)	6.6 (0.6)	0.75
LF/HF Ratio	2.2 (1.4)	2.3 (1.3)	2.2 (1.5)	0.60
SDNN (ms)	75.3 (24.5)	75.6 (25.8)	75.0 (23.2)	0.83
RMSSD (ms)	48.9 (24.1)	47.7 (24.4)	50.1 (23.9)	0.37
Heart Rate (BPM)	82.2 (11.3)	83.0 (11.5)	81.3 (11.1)	0.20

Abbreviations: HF, high-frequency power; HRV, heart rate variability; LF, low-frequency power; Log, logarithm; RMSSD, square root of the mean of the sum of the squares of differences between adjacent RR intervals; SDB, sleep disorder breathing; SDNN, standard deviation of all RR intervals.
* Overall average of the intra-subject means.

Table 2
Regression coefficient of the overall (39 h) HRV in association with sleep variability variables.

Sleep Variables		HRV Index					
		Log-HF (ms^2) β (SE)	Log LF (ms^2) β (SE)	LF/HF ratio β (SE)	SDNN (ms) β (SE)	RMSSD (ms) β (SE)	HR (bpm) β (SE)
Mean Duration	M1	–0.05 (0.03)	–0.05 (0.02)**	0.02 (0.03)	–1.08 (0.63)	–0.80 (0.92)	–0.12 (0.33)
Duration Variability		–0.17 (0.04)**	–0.15 (0.02)**	0.09 (0.04)*	–7.06 (0.91)**	–5.43 (1.32)**	2.42 (0.48)**
	M2	–0.06 (0.03)*	–0.05 (0.01)**	0.05 (0.03)	–1.00 (0.66)	–0.91 (0.95)	–0.21 (0.34)
		–0.14 (0.04)**	–0.12 (0.02)**	0.07 (0.04)	–6.0 (0.92)**	–4.94 (1.33)**	2.44 (0.48)**
Mean Efficiency	M1	–0.07 (0.04)	–0.09 (0.02)**	–0.01 (0.04)	–3.33 (0.96)**	–1.50 (1.39)	0.52 (0.51)
Efficiency Variability		–0.26 (0.06)**	–0.19 (0.03)**	0.15 (0.06)*	–7.99 (1.40)**	–5.89 (2.01)**	3.06 (0.73)**
	M2	–0.04 (0.04)	–0.07 (0.02)**	–0.05 (0.04)	–2.22 (1.00)*	–0.64 (1.45)	0.88 (0.51)
		–0.22 (0.06)**	–0.17 (0.03)**	0.10 (0.06)	–6.58 (1.41)**	–4.76 (2.04)*	3.46 (0.72)**

Abbreviations: HF, high-frequency power; HRV, heart rate variability; LF, low-frequency power; Log, logarithm; RMSSD, square root of the mean of the sum of the squares of differences between adjacent RR intervals; SDNN, standard deviation of all RR intervals; M1, Unadjusted model; M2, Adjusted model for age, race, sex, and BMI percentile.
Results were expressed as 1-h increase in sleep duration, duration variability, and 10% increase in sleep efficiency and its variability.
* $p < 0.05$.
** $p < 0.01$.

was significantly lower than for females, which were 6.8(0.8) h and 7.1(0.9) h, respectively. The average sleep duration during weekdays was 6.9 h (ranging from 3.8 to 10.1 h), whereas the weekend average sleep duration was 7.2 h (ranging from 1.8 to 10.5 h). Females slept significantly more than males during the weekdays. It indicated that the habitual sleep variability was mostly influenced by the weekday and weekend variation in sleep duration. In addition, habitual sleep efficiency was significantly higher in female than in males (83.9(5.3)% vs. 81.4(6.7)%). We did not find a statistically significant gender difference in sleep duration variability or efficiency variability. In addition, no statistically significant difference was found between genders on any of the HRV variables.

3.2. Sleep variability and its effect on 39-h, daytime, and nighttime HRV indices

The association between sleep variability variables and 39-h of HRV indices are presented in Table 2. Unadjusted and major confounders (age, sex, race, and BMI percentile) adjusted regression coefficients from linear mixed-effect models were used to report these associations. In these models, habitual sleep duration and duration variability, or habitual sleep efficiency and efficiency variability were included in the same model to control for each other. In both unadjusted and adjusted models, a 1-h increase in sleep duration variability was significantly associated with lower HF, LF, SDNN, and RMSSD, and higher HR. However, no significant association was found between increased sleep duration and HRV indices, with the exception of significantly lower LF and HF. In the unadjusted models, increased habitual sleep efficiency variability was significantly associated with lower HF, LF, SDNN, and RMSSD, and higher LF/HF ratio and HR. After adjusting for major confounders, the associations between 10% increase in sleep efficiency variability and the HRV variables and HR remained highly significant, except LF/HF ratio. Significant associations were found between 10% increase of habitual sleep efficiency and lower LF and SDNN.

Given that sleep variability variables were significantly related to HRV over the entire study period, we decided to further investigate the relationship between sleep variability and HRV during daytime (from 8:00AM to 8:00PM) and nighttime (from 8:00PM to 8:00AM) separately. As shown in Table 3, adjusted regression coefficients from linear mixed-effect models were used to report these associations. After the adjustment of major confounders and sleep duration, a 1-h increase in duration variability was significantly associated with both daytime and nighttime HRV indices, with the exception of daytime LF/HF ratio. However, a 1-h increase in sleep duration was only significantly associated with lower LF during nighttime. A similar pattern was found between sleep efficiency variables and HRV, where 10% increase sleep efficiency variability was significantly associated with lower HRV and higher HR in daytime and nighttime.

Table 3
Adjusted regression coefficient of daytime and nighttime HRV in association with sleep variability variables.

Sleep Variables	HRV Index					
	Log-HF (ms^2) β (SE)	Log LF (ms^2) β (SE)	LF/HF ratio β (SE)	SDNN (ms) β (SE)	RMSSD (ms) β (SE)	HR (bpm) β (SE)
Daytime (8:00AM–8:00PM)						
Mean Duration	–0.06 (0.04)	–0.04 (0.03)	0.09 (0.09)	–0.52 (1.11)	–0.41 (1.12)	–0.21 (0.59)
Duration Variability	–0.12 (0.06)*	–0.10 (0.04)**	0.10 (0.06)	–5.30 (1.54)**	–4.11 (1.55)**	2.76 (0.82)**
Mean Efficiency	–0.01 (0.07)	–0.06 (0.04)	–0.09 (0.10)	–2.51 (1.69)	–0.47 (1.70)	1.07 (0.89)
Efficiency Variability	–0.23 (0.09)*	–0.21 (0.06)**	0.02 (0.14)	–8.58 (2.39)**	–6.88 (2.41)**	4.43 (1.27)**
Nighttime (8:00PM–8:00AM)						
Mean Duration	–0.05 (0.03)	–0.05 (0.02)**	0.02 (0.03)	–1.09 (0.78)	–1.29 (1.22)	–0.24 (0.40)
Duration Variability	–0.16 (0.05)**	–0.13 (0.02)**	0.09 (0.04)*	–6.37 (1.08)**	–5.29 (1.69)**	2.21 (0.55)**
Mean Efficiency	–0.04 (0.05)	–0.08 (0.03)**	–0.034 (0.04)	–1.84 (1.16)	–0.60 (1.81)	0.76 (0.58)
Efficiency Variability	–0.20 (0.07)**	–0.16 (0.04)**	0.14 (0.06)*	–5.61 (1.63)**	–3.87 (2.56)	2.97 (0.82)**

Abbreviations: HF, high-frequency power; HRV, heart rate variability; LF, low-frequency power; Log, logarithm; RMSSD, square root of the mean of the sum of the squares of differences between adjacent RR intervals; SDNN, standard deviation of all RR intervals.
All models were adjusted for age, race, sex, and BMI percentile.
Results were expressed as 1-h increase in sleep duration, duration variability, and 10% increase in sleep efficiency and its variability.
* $p < 0.05$.
** $p < 0.01$.

In summary, increase in both objectively measured habitual sleep duration variability and efficiency variability were significantly associated with lower HRV and higher HR for 39-h, daytime, and nighttime. However, habitual sleep duration and efficiency were not consistently related to HRV in this sample of healthy adolescents.

4. Discussion

Previous studies have reported an inconsistent relationship between subjectively measured sleep duration and cardiac autonomic dysfunction [15,16]. Specifically, Sampei and coworkers reported that subjectively reported short sleep duration is related to impaired CAM [15]. However, Michels et al. found that subjectively measured sleep duration was not related to HRV [16]. More important, it has been argued that subjectively measured sleep duration does not capture the actual sleep duration, as it is weakly correlated with objectively measured sleep duration [34]. Our group has suggested that subjectively reported sleep duration is a marker of emotional stress [35]. On the other hand, the association between objectively measured sleep pattern and CAM has been rarely investigated. Therefore, we examined the relationship between objectively measured habitual sleep patterns and CAM, as measured by HRV indices and HR. Comparing to the previous study by Michels et al. [16], in which they also found that objectively measured sleep duration was associated with lower HF and LF, we observed a similar pattern between objectively measured sleep duration and HRV. However, the most important finding from our study was that higher habitual sleep duration variability and efficiency variability, as measured by actigraph over multiple nights, showed a more consistent and stronger association with lower HRV than average sleep duration and efficiency, in this sample of healthy adolescents. The strong and consistent associations remained significant even after adjusting for habitual sleep duration and efficiency. It indicated that the habitual sleep duration variability and efficiency variability are the most prominent predictors of HRV, instead of sleep duration and efficiency.

HRV reflects the heart's ability to respond to physiological and environmental stimuli. In adults, lower HRV has been associated with a higher risk of all-cause mortality [26,32,36–38], sudden cardiac death [39], and risk of developing coronary heart disease [28–30,36–38,40–43]. Previous studies also reported an association between lower HRV and sleep deprivation [7,44]. The vast majority of the previous studies suggested that increased sleep duration is associated with a decrease in sympathetic activity in healthy adults [45–48], although some studies showed conflicting results [49,50]. In addition, low sleep efficiency has been associated with lower parasympathetic and higher sympathetic activity [51,52]. In children, lower HRV has been associated with cardiovascular risk factor, such as high blood pressure and obesity [53]. Furthermore, an increased risk of CVD was seen in adolescents with high sleep disturbance [28]. Therefore, acquiring enough sleep and improving sleep efficiency may result in a more favorable HRV profile and consequently reduce CVD risks in adolescents and adults.

In addition to the average sleep duration and efficiency, the variability of sleep duration and of efficiency play as critical components of habitual sleep pattern. Objectively measured sleep duration variability has been increasingly investigated in sleep research [18,19,54]. Previous studies have revealed that the sleep duration over multiple nights is highly variable within individuals [54]. In general, the habitual sleep duration variability across multiple nights may contribute to an individual's perceptions of sleep quality [18]. More important, high variability of sleep pattern may contribute to sleep and psychological problems [17–21]. For example, objectively measured sleep duration variability over seven nights has been related to insomnia [19]. Moreover, previous findings from our group have suggested that insomnia is an independent risk factor for impaired CAM in children. For instance, we reported that insomnia symptoms are related to higher sympathetic and lower parasympathetic cardiac outflow in children [23]. Therefore, it is plausible that high variability in sleep duration and efficiency may lead to impaired cardiac autonomic function. Our findings supported this hypothesis and suggested that the variability of sleep pattern had a more consistent and stronger impact on CAM than the mean sleep pattern. Thus, it is of great importance to establish and maintain a regular habitual sleep pattern.

A few limitations of this study should be recognized. First, the use of cross-sectional data limited our ability to establish a temporal relationship. Thus, our results support the need for future longitudinal studies to investigate the effect of habitual sleep patterns on CAM. Second, because of the accelerometers' low specificity, actigraphy is not the gold standard in measuring sleep duration. However, it has been proven as a valid cost-effective and noninvasive tool to measure sleep duration in previous epidemiological studies [16,18,19]. Third, participants were instructed to wear the actigraph on their nondominant wrist before going to bed at night. There is a possibility that some may have forgotten to wear it. However, the actigraph data were reviewed by investigators to remove artifacts and confirm compliance based on participants' daily logs. To minimize the impact of noncompliance, we further excluded those subjects with <5 nights actigraph data.

Important strengths of this study are worth mentioning. First, it is the first population-based sample of adolescents investigating the association between habitual sleep duration variability and efficiency variability on CAM. Second, we were able to collect long duration of ECG recording (39-h of beat-to-beat ECG data). Third, we used the seven-night actigraphy as an objective measurement of habitual sleep pattern. Other methods, including the 24-h actigraphy or one-night PSG in laboratory, may not reflect the habitual sleep pattern and limit its generalizability to real life. Fourth, we purposely included the mean sleep pattern and its variability in the same regression models to control for each other. The more consistent and stronger association between sleep variability variables and HRV suggested the key impact of habitual sleep duration variability and efficiency variability on CAM.

In conclusion, our findings demonstrate that higher objectively measured habitual sleep duration variability and efficiency variability are associated with impaired HRV and higher HR in healthy adolescents. These data support the need for establishing and maintaining a regular sleep pattern to prevent the onset of CVD later in life, even in young adolescents.

Conflict of interest

The authors declare that they have no competing interests.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.10.007.

Authors' contributions

Sol M Rodríguez-Colón collected the data, did the analysis, interpreted the data, and drafted the manuscript. Fan He collected the data, did the analysis, and interpreted the data. Edward O. Bixler participated in the writing of the manuscript. Julio Fernandez-Mendoza provided comments for the revision of the manuscript. Alexandros N. Vgontzas provided comments for the revision of the manuscript. Susan Calhoun provided comments for the revision of the manuscript. Zhi-Jie Zheng provided comments for the revision of the manuscript. Duanping Liao provided overall direction of the manuscript, participated in the interpretation of the study data and the writing of the manuscript. All authors read and approved the final manuscript.

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References

[1] Cappuccio FP, Stranges S, Kandala NB, Miller MA, Taggart FM, Kumari M, et al. Gender-specific associations of short sleep duration with prevalent and incident hypertension: the Whitehall II Study. Hypertension 2007;50:693–700.
[2] Knutson KL. Sleep duration and cardiometabolic risk: a review of the epidemiologic evidence. Best Pract Res Clin Endocrinol Metab 2010;24:731–43.
[3] Nagai M, Hoshide S, Kario K. Sleep duration as a risk factor for cardiovascular disease-a review of the recent literature. Curr Cardiol Rev 2010;6:54–61.
[4] Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care 2010;33:414–20.
[5] Kaneita Y, Uchiyama M, Yoshiike N, Ohida T. Associations of usual sleep duration with serum lipid and lipoprotein levels. Sleep 2008;31:645–52.
[6] Cappuccio FP, Taggart FM, Kandala NB, Currie A, Peile E, Stranges S, et al. Meta-analysis of short sleep duration and obesity in children and adults. Sleep 2008;31:619–26.
[7] Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Eur Heart J 2011;32:1484–92.
[8] Carskadon MA, Wolfson AR, Acebo C, Tzischinsky O, Seifer R. Adolescent sleep patterns, circadian timing, and sleepiness at a transition to early school days. Sleep 1998;21:871–81.
[9] Meijer AM, Habekothe HT, Van den Wittenboer GLH. Time in bed, quality of sleep and school functioning of children. J Sleep Res 2000;9:145–53.
[10] Tynjala J, Kannas L, Valimaa R. How young Europeans sleep. Health Educ Res 1993;8:69–80.
[11] Gradisar M, Gardner G, Dohnt H. Recent worldwide sleep patterns and problems during adolescence: a review and meta analysis of age, region, and sleep. Sleep Med 2011;12:110–18.
[12] Guilleminault C, Lugaresi E, editors. Evolution of sleep and daytime sleepiness in adolescents. In: Sleep/wake disorders: natural history, epidemiology, and long-term evolution. New York (NY): Raven Press; 1983. p. 201–16.
[13] Mindell J, Owens JA. Clinical guide to pediatric sleep: diagnosis and management of sleep problems. Philadelphia, USA: Lippincott Williams & Wilkins; 2003.
[14] National Sleep Foundation. Summary findings of the 2004 Sleep America Poll. Washington DC: National Sleep Foundation; 2004.
[15] Sampei M, Murata K, Dakeishi M, Wood DC. Cardiac autonomic hypofunction in preschool children with short nocturnal sleep. Tohoku J Exp Med 2006;208:235–42.
[16] Michels N, Clays E, De Buyzere M, Vanaelst B, De Henauw S, Sioen I. Children's sleep and autonomic function: low sleep quality has an impact on heart rate variability. Sleep 2013;36(12):1939–46.
[17] Billiard M, Alperovitch A, Perot C, Jammes A. Excessive daytime somnolence in young men: prevalence and contributing factors. Sleep 1987;10:297–305.
[18] Lemola S, Ledermann T, Friedman EM. Variability of sleep duration is related to subjective sleep quality and subjective well-being: an actigraphy study. PLoS ONE 2013;8(8):e71292.
[19] Buysse DJ, Cheng Y, Germain A, Moul DE, Franzen PL, Fletcher M, et al. Night-to-night sleep variability in older adults with and without chronic insomnia. Sleep Med 2010;11:56–64.
[20] Harvey AG. A cognitive model of insomnia. Behav Res Ther 2002;40:869–93.
[21] Wohlgemuth WK, Edinger JD, Fins AI, Sullivan RJ. How many nights are enough? The short-term stability of sleep parameters in elderly insomniacs and normal sleepers. Psychophysiology 1999;36:233–44.
[22] Rodríguez-Colón S, He F, Shaffer M, Li X, Vgontzas AN, Bixler EO, et al. Insomnia symptoms and sleep duration are associated with impaired Cardiac Autonomic Modulation in children. Neurosci Med 2011;2(3):288–94.
[23] Perlis ML, McCall WV, Jungquist CR, Pigeon WR, Matteson SE. Placebo effects in primary insomnia. Sleep Med Rev 2005;9:381–9.
[24] Vallieres A, Ivers H, Bastien CH, Beaulieu-Bonneau S, Morin CM. Variability and predictability in sleep patterns of chronic insomniacs. J Sleep Res 2005;14:447–53.
[25] Kleiger RE, Stein PK, Bigger JT. Heart rate variability: measurement and clinical utility. Ann Noninvasive Electrocardiol 2005;10:88–101.
[26] Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987;59:256–62.
[27] Zuanetti G, Neilson JM, Latini R, Santoro E, Maggioni AP, Ewing DJ. Prognostic significance of heart rate variability in post-myocardial infarction patients in the fibrinolytic era. The GISSI-2 results. Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico. Circulation 1996;94:432–6.
[28] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043–65.
[29] Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, et al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation 1996;94(11):2850–5.
[30] Stein PK, Barzilay JI, Chaves PH, Domitrovich PP, Gottdiener JS. Heart rate variability and its changes over 5 years in older adults. Age Ageing 2009;38(2):212–18.
[31] Liao D, Barnes RW, Chambless LE, Simpson RJ Jr, Sorlie P, Heiss G. Population based study of heart rate variability and prevalent myocardial infarction – The ARIC Study. J Electrocardiol 1996;29:189–98.
[32] Dekker JM, Crow RS, Folsom AR, Hannan PJ, Liao D, Swenne CA, et al. Low heart rate variability in a two minute rhythm strip predicts risk of coronary heart disease and mortality from several causes – The ARIC Study. Circulation 2000;102:1239–44.
[33] Niskanen JP, Tarvainen MP, Ranta-Aho PO, Karjalainen PA. Software for advanced HRV analysis. Comput Methods Programs Biomed 2004;76(1):73–81.
[34] Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ. Self-reported and measured sleep duration: how similar are they? Epidemiology 2008;19(6):838–45.
[35] Vgontzas AN, Bixler EO. Short sleep and obesity: are poor sleep, chronic stress, and unhealthy behaviors the link? Sleep 2008;31(9):1203.
[36] Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213:220–2.
[37] Hayano J, Sakakibara Y, Yamada A, Yamada M, Mukai S, Fujinami T, et al. Accuracy of assessment of cardiac parasympathetic tone by heart rate variability in normal subjects. Am J Cardiol 1991;67:199–204.
[38] Kamath MV, Ghista DN, Fallen EL, Fitchett D, Miller D, McKelvie R. Heart rate variability power spectrogram as a potential noninvasive signature of cardiac regulatory system response, mechanisms, and disorders. Heart Vessels 1987;3:33–41.
[39] Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-parasympathetic interaction in man and conscious dog. Circ Res 1986;59:178–93.
[40] Pomeranz B, Macaulay RJ, Caudill MA, Kutz I, Adam D, Gordon D, et al. Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol 1985;248:H151–3.
[41] Martin GJ, Magid NM, Myers G, Barnett PS, Schaad JW, Weiss JS, et al. Heart rate variability and sudden death secondary to coronary artery disease during ambulatory electrocardiographic monitoring. Am J Cardiol 1987;60:86–9.
[42] Liao D, Cai J, Rosamond W, Barnes RW, Hutchinson RG, Whitsel EA, et al. Cardiac autonomic function and incident CHD: a population based case-cohort study – The ARIC Study. Am J Epidemiol 1997;145:696–706.
[43] Liao D, Carnethon MR, Evans GW, Cascio WE, Heiss G. Lower heart rate variability is associated with the development of coronary heart disease in individuals with diabetes – the ARIC study. Diabetes 2000;51:3524–31.
[44] Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol 2010;141:122–31.
[45] Burgess HJ, Trinder J, Kim Y, Luke D. Sleep and circadian influences on cardiac autonomic nervous system activity. Am J Physiol 1997;273:H1761–8, 25.
[46] Burgess HJ, Trinder J, Kim Y. Cardiac autonomic nervous system activity during presleep wakefulness and stage 2 NREM sleep. J Sleep Res 1999;8:113–22, 26.
[47] Somers VK, Dyken E, Mark AL, Abboud FM. Sympathetic nerve activity during sleep in normal subjects. N Engl J Med 1993;328:303–7, 27.
[48] Otzenberger H, Gronfier C, Simon C, Charloux A, Ehrhart J, Piquard F, et al. Dynamic heart rate variability: a tool for exploring sympathovagal balance continuously during sleep in men. Am J Physiol 1998;275:H946–50.
[49] Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet 1999;354:1435–9.
[50] Vaara J, Kyrolainen H, Koivu M, Tulppo M, Finni T. The effect of 60-h sleep deprivation on cardiovascular regulation and body temperature. Eur J Appl Physiol 2009;105:439–44.
[51] Zhong X, Hilton HJ, Gates GJ, Jelic S, Stern Y, Bartels MN, et al. Increased sympathetic and decreased parasympathetic cardiovascular modulation in normal humans with acute sleep deprivation. J Appl Physiol 2005;98:2024–32.
[52] Glos M, Fietze I, Blau A, Baumann G, Penzel T. Cardiac autonomic modulation and sleepiness: physiological consequences of sleep deprivation due to 40 h of prolonged wakefulness. Physiol Behav 2014;125:45–53.
[53] Zhou Y, Xie GL, Wang JH, Yang SR. Cardiovascular risk factors significantly correlate with autonomic nervous system activity in children. Can J Cardiol 2012;28:477–82.
[54] Knutson KL, Rathouz PJ, Yan LL, Liu K, Lauderdale DS. Intraindividual daily and yearly variability in actigraphically recorded sleep measures: the CARDIA study. Sleep 2007;30:793–6.